Co-grafts of Human Embryonic Stem Cell Derived Retina Organoids and Retinal Pigment Epithelium for Retinal Reconstruction in Immunodeficient Retinal Degenerate Royal College of Surgeons Rats.

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Public Summary:
Retinal degenerative (RD) diseases that target photoreceptors and/or the adjacent retinal pigment epithelium (RPE) affect millions of people. For those suffering from currently incurable RD diseases such as age-related macular degeneration and retinitis pigmentosa, stem cell-based therapy is being pursued as a potential approach. In most RD diseases, both RPE and photoreceptors are degenerated and or dysfunctional. Hence, it is suggestive that a combination therapy involving both photoreceptors and RPE is a requisite for achieving meaningful benefits. In previous studies, co-grafted sheets of fetal retina with RPE have demonstrated vision improvement, but this has not yet been attempted with stem-cell derived tissue. Here we demonstrate a cellular therapy for irreversible retinal eye injuries using a 'total retina patch' made of photoreceptor progenitor sheets and healthy RPE cells by employing tissue engineering technique. In vivo transplantation experiments conducted in immunodeficient retinal degenerate Royal College of Surgeons rats showed structural reconstruction of the severely damaged retina. Long-term survival of the co-graft in the rat subretinal space and improvement in visual function were observed based on histology examination, in vivo imaging, and vision testing. This new co-graft transplantation approach can be considered as a new therapy for complete replacement of a degenerated retina.

Scientific Abstract:
End-stage age-related macular degeneration (AMD) and retinitis pigmentosa (RP) are two major retinal degenerative (RD) conditions that result in irreversible vision loss. Permanent eye damage can also occur in battlefields or due to accidents. This suggests there is an unmet need for developing effective strategies for treating permanent retinal damages. In previous studies, co-grafted sheets of fetal retina with its retinal pigment epithelium (RPE) have demonstrated vision improvement in rat retinal disease models and in patients, but this has not yet been attempted with stem-cell derived tissue. Here we demonstrate a cellular therapy for irreversible retinal eye injuries using a "total retina patch" consisting of retinal photoreceptor progenitor sheets and healthy RPE cells on an artificial Bruch's membrane (BM). For this, retina organoids (ROs) (cultured in suspension) and polarized RPE sheets (cultured on an ultrathin parylene substrate) were made into a co-graft using bio-adhesives [gelatin, growth factor-reduced matrigel, and medium viscosity (MVG) alginate]. In vivo transplantation experiments were conducted in immunodeficient Royal College of Surgeons (RCS) rats at advanced stages of retinal degeneration. Structural reconstruction of the severely damaged retina was observed based on histological assessments and optical coherence tomography (OCT) imaging. Visual functional assessments were conducted by optokinetic behavioral testing and superior colliculus electrophysiology. Long-term survival of the co-graft in the rat subretinal space and improvement in visual function were observed. Immunohistochemistry showed that co-grafts grew, generated new photoreceptors and developed neuronal processes that were integrated into the host retina. This novel approach can be considered as a new therapy for complete replacement of a degenerated retina.